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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHERNYSHEV, OLGA N	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 03/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/665,350	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 39-51 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 39-51 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4, 12 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election of species in Paper No. 13 is acknowledged. However, during further examination, the requirement for election of species has been reconsidered and withdrawn. Claims 39-51 are pending and under examination in the instant office action.

Sequence compliance

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825. Specifically, no sequence listing has been provided which includes the amino acid sequence presented in line 37 on page 2 and line 17 on page 14 of the instant specification. Applicant needs to provide a substitute computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences that are present in the instant application and encompassed by these rules, a substitute paper copy of that "Sequence Listing", an amendment directing the entry of that paper copy into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. §§ 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). The instant specification will also need to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. For rules interpretation Applicant may call (703) 308-1123. See M.P.E.P. 2422.04.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.The oath or declaration is defective because:

Perhaps, the printout of the declaration had a line shift, which resulted in misplacing address information as well as citizenship of each inventor. Therefore, in most cases the oath does not identify the mailing or post office address and citizenship of each inventor. A mailing or post office address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing or post office address should include the ZIP Code designation. The mailing or post office address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

4. Further, the oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration of inventor Wei-Qiang Gao. See 37 CFR 1.52(c).

Specification

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (page 71, line 28, for example). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

6. Tables 1-5 of the instant specification do not comply with 37 C.F.R. 1.52 (b) with respect to font size. 37 C.F.R. 1.52 (b) states that:

" Except for drawings, the application papers (specification, including claims, abstract, oath or declaration, and papers as provided for in this part) and also papers subsequently filed, must have each page plainly written on only one side of a sheet of paper, with the claim or claims commencing on a separate sheet and the abstract commencing on a separate sheet. See §§ 1.72(b) and 1.75(h). The sheets of paper must be the same size and either 21.0 cm. by 29.7 cm. (DIN size A4) or 21.6 cm. by 27.9 cm. (8 ½ by 11 inches). Each sheet must include a top margin of at least 2.0 cm. (3/4 inch), a left side margin of at least 2.5 cm. (1 inch), a right side margin of at least 2.0 cm. (3/4 inch), and a bottom margin of at least 2.0 cm. (3/4 inch), and no holes should be made in the sheets as submitted. The lines of the specification, and any amendments to the specification, must be 1 ½ or double spaced. The pages of the specification including claims and abstract must be numbered consecutively, starting with 1, the numbers being centrally located above or preferably, below, the text. See § 1.84 for drawings.
37 C.F.R. 1.58 (c) states that:

Chemical and mathematical formulae and tables must be presented in compliance with § 1.52(a) and (b), except that chemical and mathematical formulae or tables may be placed in a landscape orientation if they cannot be presented satisfactorily in a portrait orientation. Typewritten characters used in such formulae and tables must be chosen from a block (nonscript) type font or lettering style having capital letters which are at least 0.21 cm. (0.08 inch) high (e.g., elite type). A space at least 0.64 cm. (1/4 inch) high should be provided between complex formulae and tables and the text. Tables should have the lines and columns of data closely spaced to conserve space, consistent with a high degree of legibility.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 39-51 are rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility. The instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby. The instant application does not disclose the biological role of this protein or its significance.

It is clear from the instant application that the protein described therein is what is termed an "orphan protein" in the art. The DNA of the instant application has been isolated because of its similarity to a known DNA. There is little doubt that, after complete characterization, this DNA and encoded protein may be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediate obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion".

The instant claims are drawn to an isolated polypeptide of as yet undetermined function or biological significance. It is clear from the instant specification that the claimed novel polypeptides are "having homology to FGF-8 [...] designated PRO187 polypeptides" (page 6, lines 25-26 of the instant specification). More specifically, "it is [...] believed that PRO187 polypeptide disclosed in the present application is a newly identified member of the FGF-8

protein family and may possess [...] activity or property typical of the FGF-8-like protein family" (page 100, lines 17-19, emphasis added). Such activities include implication "in cellular differentiation and embriogenesis, including the patterning which appears during limb formation. FGF-8 and the PRO187 molecules of the invention therefore are likely to have potent effects on cell growth and development" (page 131, lines 17-20, emphasis added). Thus, based on the structural similarities to different known proteins with known or proposed function, it has been suggested that the PRO187 of the instant invention would also possess similar biological activity. Numerous publications exist on a topic of predicting protein functions from structural similarities or homology to the known proteins. It is well described in the art that amino acid structure cannot necessarily predict the function of the protein: "Knowing the protein structure by itself is insufficient to annotate a number of functional classes and is also insufficient for annotating the specific details of protein function" (see Skolnick et al., Box 2 on page 36 and the whole paper). Moreover, "Structural similarity does not necessarily mean a common evolutionary origin and homologous sequences may evolve into different folds (according to current classification schemes) (See Bork et al., Current Opinion in structural Biology, 1998, 8, page 332, first column, second paragraph). Thus, according to the state of the art, functional characteristics of a protein cannot be unequivocally extrapolated from its structural characteristics. Because the various members of the FGF family have diverse and different biological activity, one cannot predict that a protein of the instant invention will possess any particular activity based solely upon its structural similarity to members of FGF family.

In the absence of knowledge of the biological significance of this specific polypeptide, there is no immediately obvious patentable use for it. According to the specification of the

instant application "[d]isease which relate to cellular growth and differentiation are [...] suitable targets for therapeutics based on functionally similar to FGF-8. For example, disease related to growth or survival of nerve cells including Parkinson's disease, Alzheimer's disease, ALS, neuropathies. Additionally, disease related to uncontrolled cell growth, e.g., cancer, would also be expected therapeutic targets" (page 19, lines 6-15 of the instant specification). The instant specification fails to provide any evidence or sound scientific reasoning that would support a conclusion that the instant nucleic acid or encoded protein is associated with any diseases or disorder. Examples 66 and 89 of the instant specification (page 204 and 217, respectively), which present information about the ability of PRO187 to inhibit VEGF stimulated proliferation of endothelial cells and or to affect glucose or FFA uptake by skeletal muscle cells fail to provide logical explanation how these data lead to the assertion of specific and substantial utility of the claimed PRO187 in treatment of cancer or diabetes. Based on analysis of the presented data and knowledge in the art, a skilled artisan would not have reasonable expectations that, for example, administration of PRO187 polypeptide would affect a rate of growth of tumor cells or glucose uptake of skeletal muscles in cancer or diabetic patients. Moreover, one skilled in the art readily recognizes that results of the *in vitro* experiments cannot be simply extrapolated into *in vivo* practice. This is especially true when it comes to growth factors, to which the claimed PRO187 is asserted to be associated with. Number of clinical trials based on promising *in vitro* results with different growth factors have failed, as have been reported in the numerous publications on the topic (see, for example, Neurotrophic factors enter the clinic, Science, 1994, 264, pp. 772-773)

Further, to employ the polypeptides of the instant invention in "assays to identify other proteins or molecules involved in binding interactions", as suggested in the instant specification

(page 124, lines 23-24) is not a specific and substantial utility and is not a "real world" because it would eventually relate to a protein for which no biological function is known. The instant application also fails to demonstrate use of the protein as a marker for any disease or condition (which would be a real world use). Because the instant specification does not teach a biological activity of the protein, one cannot employ it to prevent or treat a condition or disease as implied by the specification. To employ polypeptides of the instant invention in any of the disclosed methods would clearly be using it as the object of further research, which has been determined by the courts to be a utility, which, alone, does not support patentability. Since the instant specification does not disclose a credible "real world" use for the encoded protein then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 39-51 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a clear asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

9. Claims 39-43 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 39-43 are directed to isolated polypeptides which have 80%, 85%, 90%, 95% and 99% identity to an amino acid sequence having SEQ ID NO: 23 or to an amino acid sequence encoded by cDNA contained in an ATCC Deposit. However, the instant specification fails to describe the entire genus of nucleic acids, which are encompassed by these claims. In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicant has possession of and what Applicant is claiming. From the specification, it is clear that Applicant has possession of a nucleic acid molecule, which encodes a protein having the amino acid sequence of SEQ ID NO: 23. This nucleic acid molecule is deposited under ATCC accession No. 209375. The subject matter, which is claimed, is described above. First, a determination of the level of predictability in the art must be made in that whether the level of skill in the art leads to a predictability of structure; and/or whether teachings in the application or prior art lead to a predictability of structure. The claims are isolated polypeptides which have 80%, 85%, 90%, 95% and 99% identity to an amino acid sequence having SEQ ID NO: 23 or to an amino acid sequence encoded by cDNA contained in an ATCC Deposit. First, the claims are not limited to a polypeptide with a specific amino acid sequence. The claims only require the amino acid sequence to share some degree of structural similarity to the isolated polypeptide of SEQ ID NO: 23. The specification only describes a polypeptide having the amino acid sequence of SEQ ID NO: 23 and fails to

teach or describe any other polypeptide which lacks the amino acid sequence of SEQ ID NO: 23 and has the activities possessed by the isolated polypeptide. Therefore, there is a lack of guidance or teaching regarding structure and function because there is only a single example provided in the specification and because there is no guidance found in the prior art.

Next in making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, each claimed species and genus must be evaluated to determine whether there is sufficient written description to inform a skilled artisan that applicant was in possession of the claimed invention at the time the application was filed. With this regard, the instant application fails to provide a written description of the species or the genus which are encompassed by the instant claims except for the polypeptide of SEQ ID NO: 23. The specification does not provide a complete structure of those isolated polypeptides which have 80%, 85%, 90%, 95% and 99% identity to an amino acid sequence having SEQ ID NO: 23 or to an amino acid sequence encoded by cDNA contained in an ATCC Deposit. The claims also fail to recite other relevant identifying characteristics (physical and/or chemical and/or functional characteristics coupled with a known or disclosed correlation between function and structure) sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. The specification fails to provide a representative number of species for the claimed genus (those isolated polypeptides which have 80%, 85%, 90%, 95% and 99% identity to an amino acid sequence having SEQ ID NO: 23 or to an amino acid sequence encoded by cDNA contained in an ATCC Deposit) because the specification teaches only the one embodiment of SEQ ID NO: 23. Therefore, the claims are directed subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

10. Claims 39-44 and 49 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

These claims expressly require the novel vectors and/or microorganisms recited therein. Since the microorganism is essential to the claimed invention it must be readily available to the public. The enablement requirements of 35 USC § 112 may be satisfied by a deposit of the plasmid and/or microorganism. Accordingly, it is deemed that a deposit of these plasmids and/or microorganisms should have been made in accordance with 37 C.F.R. 1.801-1.809.

It is noted that applicants have deposited the organism but there is not indication in the specification as to public availability. If the deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 39-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Claims 39-44 in parts b-d and claims 46-48 are vague and indefinite for recitation of "associated signal peptide" and "extracellular domain" claimed to be shown in Figure 11. However, Figure 11 does not indicate the claimed sequences. Clarification is required.

13. Claims 45 and 49-52 are indefinite for being dependent form indefinite claims.

Conclusion

14. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (703) 305-1003. The examiner can normally be reached on Monday to Friday 9 AM to 5 PM ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (703) 308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 782-9306 for regular communications and (703) 782-9307 for After Final communications.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices

published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)0. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 308-4556 or (703) 308-4242. If either of these numbers is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Official papers should NOT be faxed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Olga N. Chernyshev, Ph.D.
March 4, 2003 OC

JOHN ULM
PRIMARY EXAMINER
GROUP 1800